REMARKS

Claims 70-121 were be pending. Claims 80, 91, 103, 115, 117, and 118 have been amended. Accordingly, claims 70-121 are pending in the application.

No additional search is required and no new issues have been raised by the amendments made herein; support for the amendments made can be found in the specification as filed and/or in the claims as previously pending. Specific support is outlined below. Furthermore, in view of the amendments and arguments set forth herein, the number of issues for appeal have been reduced. It is believed that the Examiner's rejections under 35 U.S.C. §112, first and second paragraph and 35 U.S.C. §102 have been obviated. Therefore, the claim amendments and cancellations made herein are permissible under 37 C.F.R. §1.116 as reducing the number of issues for appeal, and Applicants respectfully request that the present Amendment be entered.

Support for the amendment to claims 80, 91, 102, 115, 117, and 118 to include the the phrase "produced by a hybridoma" can be found throught the specification, e.g., at page 6, line 21. This amendment merely clarifys that the previously searched ATCC accession numbers refer to hybridomas and not antibodies.

No new matter has been added. A version of the amendments showing changes made is attached as Appendix A.

Applicants' amendment of claims should in no way be construed as an acquiescence to the Examiner's position with respect to the claims as previously pending. Applicants reserve the right to further prosecute the same or similar claims in a subsequent patent application.

The specification has been amended to include deposit dates and complete name and address of depository and to correct the figure legends. No new matter has been added by way of

these amendments. Support for the above claim amendments can be found in the application as filed and/or the claims as previously pending. A version of the amendments showing changes made is attached as Appendix A.

Claims 119-121

The Examiner states that newly added claims 119-121 have been withdrawn from consideration as being drawn to B7-1, not B7-2. Applicants note that SEQ ID NO:23 is the sequence for ***murine B7-2***, not B7-1. Accordingly, Applicants submit that claims 119-121 are embraced by the Group I invention elected by Applicants and Applicants request that claims 119-121 be reinstated.

Rejection of claims 80, 91, 103, and 115 Under 35 U.S.C. 112, first paragraph

Claims 80, 91, 103, and 115 have been rejected under 35 U.S.C. 112, first paragraph as the specification does not include the date of deposit and the complete name and adfdress of the depository. In response, the specification has been amended and copies of the deposit information for HA5.2B7 (HB11687), HF2.3D1 (HB11686), and HA3.1F9 (HB 11688) hybridomas and the deposit contract are being submitted herewith. In addition, a declaration regarding the deposits is submitted herewith. Accordingly, Applicants respectfully request that the rejection of claims 80, 91, 103, and 115 Under 35 U.S.C. 112, first paragraph be reconsidered and withdrawn.

Rejection of claims 80, 91, 103, and 115 Under 35 U.S.C. 112, second paragraph

Claims 80, 91, 103, and 115 have been rejected under 35 U.S.C. 112, second paragraph. Claims 80, 91, 103, and 115 have been objected to as not referring to hybridomas. Claims 117-118 have been objected to as lacking proper antecedent basis for the term "agent." These rejections have been obviated by the amendments to claims 80, 91, 103, and 115 to refer to hybridomas and to claims 117-118 to change the claim dependency. Accordingly, Applicants respectfully request that the rejection of claims 80, 91, 103 and 115 under 35 USC 112, first paragraph, be reconsidered and withdrawn.

Rejection of claims 116-118 Under 35 U.S.C. 102(e)

Claims 116-118 have been rejected under 35 USC 102(e) as being anticipated by De Boer et al. 5,747,034. The Examiner states that De Boer et al. "teach methods of inhibiting immune responses both in vitro and in vivo with combinations of B7-specific inhibitors, including the use of both B7-1 specific and B7-2 specific antibodies. This rejection is respectfully traversed.

The pending claims are directed to methods of using anti-B7-2 antibodies to block binding interactions of B7-2 with CD 28 or CTLA 4 on an immune cell; to inhibit proliferation of a T cell; to inhibit cytokine production; or to downregulate immune responses.

The reference fails to teach or suggest the use of anti-B7-2 antibodies in combination with immunosuppressive agents as presently claimed. The De Boer et al. reference teaches monoclonal antibody B7-24 which "***is an unique monoclonal antibody that binds specifically to the B7-1 molecule, but not to B7-2***." The reference further states:

> This is in contrast with a recombinant fusion protein of the CTLA-4 molecule (Linsley, J. Exp. Med., 174, 561 (1991), which binds to both B7-1 and B7-2. Monoclonal antibody B7-24 is also different from the anti-B7 monoclonal antibody BB-1, which binds

> to B7-1 and in addition to a third form of the B7 molecule, B7-3 (Boussiotis et al., Proc. Nat'l. Acad. Sci. (USA), 90, 11059 (1993)). Although it is known that both B7-1 and B7-2 can co-stimulate T cells by binding to the CD28 molecule, it is not known that blocking only B7-1 with a specific monoclonal antibody such as B7-24, when combined with an immunosuppressive drug such as cyclosporin A, can induce T-cell tolerance or anergy. This is unexpected since it has been suggested in the literature that CsA can prevent anergy induction in mice ›Schwartz, Science, 248, 425 (1990).

The reference continues:

> Therefore co-administration of a molecule that specifically binds to the B7-1 molecule but not to B7-2 or B7-3 and an immunosuppressive agent that inhibits the production of IL-2 by T cells to a patient may induce long-lasting T-cell tolerance or anergy.

The reference also contains some data obtained using anti-B7-2 ***OR*** anti-B7-1 in addition to data obtained using CTLA4Ig. The reference states that the data therein "demonstrates that blocking both B7-1 and B7-2 does not result in alloantigen-specific tolerance."

Moreover, the reference also states that:

> Induction of tolerance in an in vivo model of heart transplantation in rats with CTLA-4 Ig is reported only to work when added 2 days after the tissue grafting. Starting the treatment at the same day of the grafting is not reported to result in tolerance. ***Thus, signaling by B7-2 interaction with T cells is needed for tolerance induction and the blocking effect at day 2 is due to blocking B7-1. With the B7-24 antibody, this is not a problem because in contrast to CTLA-4 Ig, it does not block B7-2.***

This passage suggests that blocking B7-2 is a problem for induction of T cell anergy as these signals are needed for tolerance induction. Therefore, the reference actually teaches away from the use of anti-B7-2 antibodies. In sum, the reference fails to teach the use of anti-B7-2

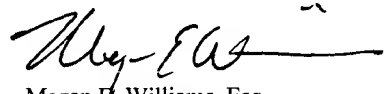
antibodies in combination with other immunosuppressive agents. Accordingly, it is respectfully requested that the rejection of claims 116-118 be reconsidered and withdrawn.

SUMMARY

If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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Dated: July 22, 2003

APPENDIX A
VERSION SHOWING CHANGES MADE

To the specification:

at page 6, please replace the paragraph beginning at line 20 with:

Another embodiment of the invention provides antibodies, preferably monoclonal antibodies, specifically reactive with a peptide of a novel B lymphocyte antigen or fusion protein as described herein. Preferred antibodies are anti-human B7-2 monoclonal antibodies produced by hybridoma cells HF2.3D1, HA5.2B7 and HA3.1F9. These hybridoma cells [have been] were deposited on July 19, 1994 with the American Type Culture Collection at 12301 Parklawn Drive, Rockville, MD 20852 as ATCC Accession No.HB 11686 (HF2.3D1), ATCC Accession No.HB 11687 (HA5.2B7), and ATCC Accession No.HB 11688 (HA3.1F9).

The Paragraph at page 9, beginning at line 3 has been amended to read:

--*Figure 8* A and B [is] are the nucleotide and deduced amino acid [sequence] sequences of the human B lymphocyte antigen B7-2 (hB7-2-clone29).--

The Paragraph at page 9, beginning at line 12 has been amended to read:

--*Figure 11*A and B are [is a] graphic [representation] representations of the proliferation of CD28+ T cells, as assessed by ^{3}H-thymidine incorporation or IL-2 secretion, to submitogenic stimulation with phorbol myristic acid (PMA) and COS cells transfected with vector alone or vectors directing the expression of either B7-1 or B7-2.

The Paragraph at page 9, beginning at line 16 has been amended to read:

Figure 12 A-G are [is a] graphic [representation] representations of the inhibition by mAbs and recombinant proteins of the proliferation of CD28+ T cells, as assessed by ^{3}H-thymidine incorporation and IL-2 secretion, to stimulation by PMA and COS cells transfected with vector alone (vector), or with a vector expressing B7-1 (B7-1) or B7-2 (B7-2). Inhibition studies were performed with the addition of either no antibody (no mAb), anti-B7 mAb 133 (133), anti-B7 mAb BB-1 (BB1), anti-B5 mAb (B5), Fab fragment of anti-CD28 (CD28 Fab), CTLA4Ig (CTLA4Ig), or Ig control protein (control Ig) to the PMA stimulated COS cell admixed $CD28^{+}$ T cells.

The Paragraph at page 9, beginning at line 24 has been amended to read:

Figure 13 A-B show [shows] the sequence homology between the human B7-2 protein (h B7-2) deduced amino acid sequence (SEQ ID NO: 2) and the amino acid sequence of both the human B7-1 protein (h B7-1) (SEQ ID NO: 28 and 29) and the murine B7-1 protein (m B7) (SEQ ID NO: 30 and 31).

The Paragraph at page 9, beginning at line 28 has been amended to read:

Figure 14 A-D are [is] the nucleotide and deduced amino acid sequence of the murine B7-2 antigen (mB7-2) (SEQ ID NO: 22 and 23).

The Paragraph at page 10, beginning at line 3 has been amended to read:

Figure 17 A-C depict [depicts] flow cytometric profiles of cells stained with an anti-hB7-2 monoclonal antibody, HA3.1F9. Cells stained with the antibody were CHO cells transfected to express human B7-2 (CHO-hB7.2), NIH 3T3 cells transfected to express human B7-2 (3T3-

hB7.2) and control transfected NIH 3T3 cells (3T3-neo). The anti-hB7.2 antibody B70 was used as a positive control.

The Paragraph at page 10, beginning at line 8 has been amended to read:

Figure 18 A-C depict [depicts] flow cytometric profiles of cells stained with an anti-hB7-2 monoclonal antibody, HA5.2B7. Cells stained with the antibody were CHO cells transfected to express human B7-2 (CHO-hB7.2), NIH 3T3 cells transfected to express human B7-2 (3T3-hB7.2) and control transfected NIH 3T3 cells (3T3-neo). The anti-hB7.2 antibody B70 was used as a positive control.

The Paragraph at page 10, beginning at line 13 has been amended to read:

Figure 19 A-C depict [depicts] flow cytometric profiles of cells stained with an anti-hB7-2 monoclonal antibody, HF2.3D1. Cells stained with the antibody were CHO cells transfected to express human B7-2 (CHO-hB7.2), NIH 3T3 cells transfected to express human B7-2 (3T3-hB7.2) and control transfected NIH 3T3 cells (3T3-neo). The anti-hB7.2 antibody B70 was used as a positive control.

The paragraph at page 34, beginning at line 32 has been amended to read:

Particularly preferred antibodies are anti-human B7-2 monoclonal antibodies produced by hybridomas HA3.1F9, HA5.2B7 and HF2.3D1. The preparation and characterization of these antibodies is described in detail in Example 8. Monoclonal antibody HA3.1F9 was determined to be of the IgG1 isotype; monoclonal antibody HA5.2B7 was determined to be of the IgG2b

isotype; and monoclonal anibody HF2.3D1 was determined to be of the IgG2a isotype. Hybidoma cells were deposited with the American Type Culture Collection 12301 Parklawn Drive, Rockville, MD 20852, which meets the requirements of the Budapest Treaty, on July 19, 1994 as ATCC Accession No.HB 11686 (HF2.3D1), ATCC Accession No.HB 11687 (HA5.2B7), and ATCC Accession No.HB 11688 (HA3.1F9).

The paragraph at page 64, beginning at line 27

has been amended to read:

Human $CD28^+$ T cells were isolated by immunomagnetic bead depletion using mAbs directed against B cells, natural killer cells, and macrophages as previously described (Gimmi, C.D., Freeman, G.J., Gribben, J.G., Gray, G., Nadler, L.M. (1993) *Proc. Natl. Acad. Sci USA* 90, 6586-6590). B7-1, B7-2, and vector transfected COS cells were harvested 72 hours after transfection, incubated with 25μg/ml of mitomycin-C for 1 hour, and then extensively washed. 10^5 $CD28^+$ T cells were incubated with 1 ng/ml of phorbol myristic acetate (PMA) and 2×10^4 COS transfectants. Blocking agents (10μg/ml) are indicated on the left side of Figure 12 and include: 1) no monoclonal antibody (no blocking agents), 2) mAb 133 (anti-B7-1 mAb), 3) mAb BB1 (anti-B7-1 and anti-B7-3 mAb), 4) mAb B5 (control IgM mAb), 5) anti-CD28 Fab (mAb 9.3), 6) CTLA-Ig, and 7) control Ig. [Panel a] Panels A-G of Figure 12 [shows] show proliferation measured by ^{3}H-thymidine (1μCi) incorporation for the last 12 hours of a 72 hour incubation. Figure

12[, panel b,] shows IL-2 production as measured by ELISA (Biosource, CA) using supernatants harvested 24 hours after the initiation of culture.

The paragraph at page 86, beginning at line 28 has been amended to read:

Three hybridomas, HA3.1F9, HA5.2B7 and HF2.3D1, were identified that produced antibodies to human B7.2-Ig. HA3.1F9 was determined to be of the IgG1 isotype, HA5.2B7 was determined to be of the IgG2b isotype and HF2.3D1 as determined to be of the IgG2a isotype. Each of these hybridomas were subcloned two additional times to insure that they were monoclonal. Hybidoma cells were deposited with the American Type Culture Collection 12301 Parklawn Drive, Rockville, MD 20852, which meets the requirements of the Budapest Treaty, on July 19, 1994 as ATCC Accession No.HB 11686 (HF2.3D1), ATCC Accession No.HB 11687 (HA5.2B7), and ATCC Accession No.HB 11688 (HA3.1F9).

To the Claims:

80. **(Amended)** The method of claim 73, wherein the antibody is produced by a hybridoma selected from the group consisting of: ATCC accession number HB 11688, ATCC accession number HB 11687, and ATCC accession number HB 11686.

91. **(Amended)** The method of claim 81, wherein the antibody is produced by a hybridoma selected from the group consisting of: ATCC accession number HB 11688, ATCC accession number HB 11687, and ATCC accession number HB 11686.

102. **(Amended)** The method of claim 93, wherein the antibody is produced by a hybridoma selected from the group consisting of: ATCC accession number HB 11688, ATCC accession number HB 11687, and ATCC accession number HB 11686.

115. **(Amended)** The method of claim 105, wherein the antibody is produced by a hybridoma selected from the group consisting of: ATCC accession number HB 11688, ATCC accession number HB 11687, and ATCC accession number HB 11686.

117. **(Amended)** The method of claim 116 [105], wherein the agent is an anti-B7-1 antibody.

118. **(Amended)** The method of claim 116 [105], wherein the agent is an immunosuppressive drug.